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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/509,418	07/11/2000	DONALD J KOROPATNICK	PM 266291	3674

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EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/509,418	KOROPATNICK ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9-16-03 has been entered.

Response to Amendment

2. The amendment to the claims filed on 9-16-03 does not comply with the requirements of 37 CFR 1.121(c) because Applicants do not include the status of every claim, for instance Applicants do not provide the status of original claims 1-14. Amendments to the claims filed on or after July 30, 2003 must comply with 37 CFR 1.121(c) which states:

> (c) *Claims.* Amendments to a claim must be made by rewriting the entire claim with all changes (*e.g.*, additions and deletions) as indicated in this subsection, except when the claim is being canceled. Each amendment document that includes a change to an existing claim, cancellation of an existing claim or addition of a new claim, must include a complete listing of all claims ever presented, including the text of all pending and withdrawn claims, in the application. The claim listing, including the text of the claims, in the amendment document will serve to replace all prior versions of the claims, in the application. In the claim listing, the status of every claim must be indicated after its claim number by using one of the following identifiers in a parenthetical expression: (Original), (Currently amended), (Canceled), (Withdrawn), (Previously presented), (New), and (Not entered).
>
> (1) *Claim listing.* All of the claims presented in a claim listing shall be presented in ascending numerical order. Consecutive claims having the same status of "canceled" or "not entered" may be aggregated into one statement (*e.g.*, Claims 1–5 (canceled)). The claim listing shall commence on a separate sheet of the amendment document and the sheet(s) that contain the text of any part of the claims shall not contain any other part of the amendment.
>
> (2) *When claim text with markings is required.* All claims being currently amended in an amendment paper shall be presented in the claim listing, indicate a status of "currently amended," and be submitted with markings to indicate the changes that have been made relative to the immediate prior version of the claims. The text of any added subject matter must be shown by underlining the added text. The text of any deleted matter must be shown by

strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. The text of any deleted subject matter must be shown by being placed within double brackets if strike-through cannot be easily perceived. Only claims having the status of "currently amended," or "withdrawn" if also being amended, shall include markings. If a withdrawn claim is currently amended, its status in the claim listing may be identified as "withdrawn—currently amended."

(3) *When claim text in clean version is required.* The text of all pending claims not being currently amended shall be presented in the claim listing in clean version, *i.e.*, without any markings in the presentation of text. The presentation of a clean version of any claim having the status of "original," "withdrawn" or "previously presented" will constitute an assertion that it has not been changed relative to the immediate prior version, except to omit markings that may have been present in the immediate prior version of the claims of the status of "withdrawn" or "previously presented." Any claim added by amendment must be indicated with the status of "new" and presented in clean version, *i.e.*, without any underlining.

(4) *When claim text shall not be presented; canceling a claim.*

(i) No claim text shall be presented for any claim in the claim listing with the status of "canceled" or "not entered."

(ii) Cancellation of a claim shall be effected by an instruction to cancel a particular claim number. Identifying the status of a claim in the claim listing as "canceled" will constitute an instruction to cancel the claim.

(5) *Reinstatement of previously canceled claim.* A claim that was previously canceled may be reinstated only by adding the claim as a "new" claim with a new claim number.

Drawings

3. New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because according to Applicants The regions of thymidylate synthase mRNA targeted by the oligonucleotides of the invention are shown in Figure 7. However, the sequence set forth in Figure 7 does not correspond to an mRNA sequence. Note the presence of Thymine (T) in the sequence set forth in Figure 7, it is well known in the art that mRNA sequences do not contain (T). An mRNA sequence normally contains Uracil (U) instead of Thymine (T). Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected

drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Sequence Listing

4. In Table 1 of the specification as filed, at page 5, Applicants amended the sequence corresponding to OLIGO 32 to recite the sequence (SEQ ID NO: 7) TTTAGGAACCGTTGGCGCAT. However, at page 23, line 16, it states that the sequence of OLIGO 32 is a randomized sequence of ODN 83, and has the following sequence: 5'-ATGCGCCAACGGTTCCTAAA-3'. However, the sequence set forth on page 23 is not included in the Sequence Listing submitted 7-23-04.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 15-20 and 29-33 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,087,489. In

the instant case an obvious-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

In the instant case, claims 1-10 of US Patent 6,087,489, recite antisense oligonucleotides of 8 to 30 nucleotides in length comprising a sequence that is complementary to a nucleic acid molecule encoding human thymidylate synthase, wherein said oligonucleotide is complementary to the 3' untranslated region of said nucleic acid molecule and inhibits the expression of said human thymidylate synthase, or wherein said oligonucleotide inhibits cell proliferation. Issued claims 2-3 recite wherein the oligonucleotide comprises SEQ ID NO: 4, this sequence is 100% identical to SEQ ID NO: 2 recited in the instant claims. Additionally, claims 4-7 of US Patent 6,087,489 recite wherein said antisense oligonucleotides contain phosphorothioate modified intersugar linkages, 2'-O-methoxyethyl and 5-methylcytosine modifications. The antisense oligonucleotides of claims 1-10 differs from claims 15-20 and 29-33 of the instant application in that these claims are not limited to: a) deoxyoligonucleotides of 8 to 50 nucleotides in length, b) compositions comprising said antisense compounds in a pharmaceutically acceptable carrier, c) a combination product comprising antisense deoxyoligonucleotides in combination with an anticancer agent.

However, it is noted that the invention of US Patent 6,087,489 encompass both oligoribonucleotides and deoxyoligonucleotides and furthermore encompass antisense

compounds from about 5 to about 50 nucleotides in length as a preferred embodiment (see col. 7, lines 1-5 and lines 12-14). Additionally, col. 15, lines 4-42, of US Patent 6,087, 489 supports compositions comprising the antisense compounds targeting thymidylate synthase including buffers, diluents and other additives for parenteral administration, and combination products thereof comprising an anticancer agent, wherein said anticancer agent is 5-fluorouracil (5-FU), 5-fluorodeoxyuridine (5-FUdR), methotrexate or Tomudex (especially col. 15, lines 25-34).

Claims 15-20 and 29-33 can not be considered patentably distinct over claims 1-10 of the issued US Patent when there are specifically disclosed embodiments in US Patent 6,087,489, which clearly indicate that claims 15-20 and 29-33 of the instant application are merely obvious variations of the invention of claims 1-10 of the referenced patent. Specifically, it would have been obvious to one of ordinary skill in the art at the time of filing to modify the antisense oligonucleotides of issued claims 1-10 by selecting specifically disclosed embodiments that support those claims, i.e. deoxyoligonucleotides that are 8 nucleotides or 50 nucleotides in length, compositions thereof and combination products, as disclosed in US 6,087,489. One having ordinary skill in the art would have been motivated to make these modifications since these embodiments are all disclosed as being obvious variations of the invention set forth in claims 1-10 of US Patent 6,087,489.

Claim Rejections - 35 USC § 112

7. Claims 15-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using antisense targeting TS mRNA to inhibit the expression of thymidylate synthase *in vitro*, does not reasonably provide enablement treating cancer in a patient such that a therapeutic effect is observed *in vivo* as a result of administering the antisense

compositions of the present invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, for the reasons of record set forth in the Office Action mailed 4-16-2003 in the rejection of claims 15-35 under 35 USC § 112, 1st paragraph.

Applicant's arguments filed 9-16-2003 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that (1) *in vivo* data is not required under 35 USC § 112, first paragraph; (2) a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as if in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Additionally, for the Examiner's information Applicants made reference to the Berg et al. (2001) journal article which describes the an *in vivo* study showing that systemic treatment with TS antisense ODN 83 significantly inhibited HT29 human colon carcinoma tumor cell growth in mice.

However, contrary to Applicant's arguments, objective evidence has been provided which raises significant reason to doubt the objective truth of Applicant's statements. Applicant's specification is not commensurate in scope with the claimed invention. Applicant's claims read on treating cancer comprising administering to a human an effective amount of antisense deoxyoligonucleotide targeting thymidylate synthase alone or in combination with an anticancer agent, however Applicant's specification provides only *in vitro* examples wherein it is demonstrated how to use the compounds and compositions of the claimed invention. However,

Applicant's specification fails to provide an adequate correlation between their *in vitro* data and predicting the behavior of the compounds of the present invention in a human. As set forth in the prior Office Action, there are a significant number of factors well known in the art, which contribute to the unpredictability associated with antisense therapy. These factors include, the controlling the fate of the nucleic acid itself once administered to an individual (volume of distribution, rate of clearance into the tissues, etc.), controlling the *in vivo* consequences of altered gene expression and protein function, the fraction of nucleic acid taken up by the target cell population, predicting the trafficking of the genetic material within cellular organelles, the rate of degradation of the nucleic acid, and the stability of the nucleic acid within a cell. Therefore, based upon these considerations, it is concluded "extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate" (See Crooke, 1998). See also, *In Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 52 USPQ2d 1129 (Fed. Cir. 1999), wherein the court held that claims in two patents directed to genetic antisense technology (which aims to control gene expression in a particular organism), were invalid because the breadth of enablement was not commensurate in scope with the claims.

In regards to the Berg et al. (2001) reference describing *in vivo* effects in a mouse by the administration of OLIGO 83, first it is noted that Applicants have not provided a copy of this reference with the response filed 9-16-2003. Secondly, the effective filing date of the instant application extends back to September 23, 1997, however the Berg et al. reference was published in 2001, and Applicants have not provided any evidence that the procedures used to practice the *in vivo* methods set forth in the Berg et al. reference were commensurate in scope with the guidance provided in the disclosure as filed, and commonly known in the art as of the effective

filing date. See MPEP § 2164[R-2] which states "The information contained in the disclosure of an application must be sufficient to inform those skilled in the relevant art how to both make and use the claimed invention." Sufficient guidance must be provided in the disclosure as filed, Applicant's post-filing reference to a published journal article is not admissible as evidence under 37 CFR § 1.132. "[A]ny analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention." MPEP § 2164.01.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Janet L. Epps-Ford, Ph.D.
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